AB066. 208. Loss of estrogen receptor (ER) through DNA methylation and alterations in molecular heterogeneity during endocrine treatment in ER-positive breast cancer

Michael Flanagan[1], Damir Varšlija[1], Sara Charmsaz[1], Nicola Cosgrove[1], Sinead Cocchiglia[1], Arnold Hill[2], Leonie Young[1]

[1]Endocrine Oncology Research Group, Department of Surgery, [2]School of Medicine & Department of Surgery, Royal College of Surgeons in Ireland, Dublin, Ireland

Background: Up to 40% of patients with estrogen receptor (ER)-positive breast cancer develop resistance to endocrine treatment, leading to progression of disease. Therapeutic pressure functionally affects oncogenes and related signalling pathways through dynamic alterations in transcriptional and epigenetic alterations. Loss of *ESR1* gene expression is a known feature of hormone therapy resistant disease. We hypothesise that estrogen/ER signalling in primary breast cancer regulates differentiation gene expression through coordinated inhibition of DNA methylation and promotion of RNA methylation. Our aim is to elucidate the mechanism by which estrogen/ER regulates gene expression and evaluate response to therapeutic pressure.

Methods: Gene expression profiling across 21 patient-matched primary breast tumours and their associated metastases was performed by TrueSeq RNA-sequencing. Cell lines and patient-derived xenograft (PDX) culture model were used to identify altered de-differentiation genes and response of *ESR1* gene to treatments afatinib (HER2-HER3), cabozantinib (pan-RTK) and an epigenetic modulator—RG108 (de-methylator). The anti-tumour activity of these treatments was assessed *ex vivo*.

Results: ER expression was unchanged following treatment with afatinib, cabozantinib and RG108. However, treatment with RG108 and tamoxifen led to a reduction in proliferation in PDX model. ESR1, a key clinically actionable gene, demonstrated consistent depletion with concomitant DNA hypermethylation in metastases compared to primary tumour and this is correlated with increases in HER2 signature.

Conclusions: Recurrent transcriptional remodelling events were identified in metastasis compared to primary tumour. An inverse correlation of crosstalk signalling was identified between ER and HER2. Further study is needed to elucidate the regulatory mechanism of ER/HER2 crosstalk, which may be epigenetically regulated through DNA and RNA methylation.

Keywords: Breast cancer; estrogen receptor; DNA methylation

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